Attachment 4

(97-009/6-5-97)

Risk Assessment Issue Paper for: Derivation of Provisional Chronic RfDs for n-Butylbenzene (CASRN 104-51-8), sec-Butylbenzene (CASRN 135-98-8), tert-Butylbenzene (CASRN 98-06-6), and n-Propylbenzene (CASRN 103-65-1)

INTRODUCTION

RfDs for n-butylbenzene, sec-butylbenzene, tert-butylbenzene, or n-propylbenzene are not listed on IRIS (U.S. EPA, 1997) or HEAST (U.S. EPA, 1995a), and have not been discussed by the RfD/RfC Work Group (U.S. EPA, 1995b). The only documents listed in the CARA database (U.S. EPA, 1991, 1994) for these chemicals are health advisories (U.S. EPA 1987a,b,c,d). The data were considered inadequate for derivation of health advisories for these chemicals. These health advisories are listed as draft documents on the Drinking Water Regulations and Health Advisories list (U.S. EPA, 1996). The butylbenzenes and n-propylbenzene were not listed in the NTP (1996, 1997) status reports, and were not the subject of ATSDR toxicological profiles (ATSDR, 1997).

Literature searches for information relevant to the toxicity and carcinogenicity of these chemicals were performed in 1991 and updated in 1993 and May 1997 and included TOXLINE (1965-1997), CANCERLINE (mid 1970s-1997), TSCATS, and RTECS.

SUMMARY OF RELEVANT INFORMATION

The only information regarding the effects of these alkylbenzenes in humans was found in NAS (1977), which stated that in humans n-propylbenzene is irritating to mucous membranes, eyes, nose, throat, and skin, and that systemically it causes depression of the central nervous system, headache, anorexia, muscular weakness, incoordination, nausea, vertigo, paresthesia, mental confusion, and unconsciousness. No information was located regarding the effects of n-butylbenzene, sec-butylbenzene, and tert-butylbenzene in humans.

NAS (1977) also summarized the results of a 6-month oral study with n-propylbenzene in rabbits, which constitutes the only information available regarding long-term effects for the requested alkylbenzenes. The study is referenced to Gerarde and Ahlstrom (1966), but unfortunately, the complete citation was not provided, and efforts to obtain the full reference proved unsuccessful. NAS (1977) states that:

> "In a 6-month subchronic oral study (Gerarde and Ahlstrom, 1966) groups of 15 rabbits were fed propylbenzene at 0.25 and 2.5 mg/kg/day. The test animals did not differ from the controls in general appearance, body weight, organ weights, and protein function of

the liver. There was a 7% decrease in red-cell count in the high-dosage group that was not significant. Hemosiderin was deposited in the spleens of the high-dosage animals, indicating red-cell destruction. There was a nonsignificant leukocyte increase in both dosage groups. Individual animals exhibited mild protein dystrophy of the liver and kidneys."

Relevant general data on alkylbenzenes were reviewed by Gerarde (1959), who indicates that liquid alkylbenzenes (the four compounds addressed in this issue paper are liquids) with short chain alkyl groups produce a warm, sharp, tingling sensation on contact with the taste buds, followed by a feeling of numbness due to local anesthesia. On contact with mucous membranes, liquid alkylbenzenes cause local irritation and vasodilation. Irritant potency decreases as the alkyl chain lengthens, but increases with branching of the alkyl side chain. Without providing data for specific compounds, Gerarde (1959) reported that in blood, alkylbenzenes are in intimate contact with endothelial cells of the blood vessels and capillaries, and local irritation of these cells results in permeability changes in the capillaries. This in turn leads to increased diapedesis, edema in surrounding tissues, petechial and gross hemorrhage.

Acute oral data were available from several sources. Two LD_{50}s for n-propylbenzene in rats were reported, 6.040 g/kg (RTECS, 1993), and 7.5 g/kg (NAS, 1977). NAS (1977) reported an LD_{50} of 5.2 g/kg for n-propylbenzene in mice. Two out of 10 rats died after administration of approximately 4.3 g/kg of n-propylbenzene or n-butylbenzene in olive oil, but 8/10 and 7/10 died after receiving the same amount of sec-butylbenzene and tert-butylbenzene in olive oil, respectively (Gerarde, 1959). Dow Chemical (1954) reported that no deaths occurred among 4 rats treated with 2 g sec-butylbenzene/kg and Sandmeyer (1981) reported an LD_{50} of 2.240 g/kg for this alkylbenzene in rats. LD_{50}s in rats for tert-butylbenzene ranged from 2.5 to 5.0 g/kg (Dupont, 1978; Rhone-Poulenc Inc., 1981; Shell Oil Company, 1979). The leading cause of death in rats in the acute oral studies conducted by Gerarde (1959) was chemical pneumonitis with pulmonary edema and hemorrhage, the latter often associated with hemorrhage in other tissues such as thymus, adrenal, and bladder. He also reported hyperemia and vasodilation of the blood vessels of the gastrointestinal tract.

The inhalation databases for these chemicals are also weak and limited to acute toxicity testing. These data are reviewed in a separate Issue Paper.

DERIVATION OF RfD

The information provided in the NAS (1977) summary for the n-propylbenzene rabbit study lacks enough detail for risk assessment purposes and, therefore, cannot be used to derive a provisional oral RfD for n-propylbenzene. Data on the oral toxicity of the other alkylbenzenes under investigation are limited to acute lethality studies which are considered inadequate for derivation of provisional RfDs for butylbenzenes.

A viable alternative is to derive an RfD by analogy to a structurally-related chemical. There are three saturated short-chain alkylbenzenes which are structurally similar to the alkylbenzenes under investigation and have RfDs on IRIS. These are summarized below:

Chemical	Critical Effect	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	RfD[a] (mg/kg-day)
Toluene	increased liver and kidney weights in rats	223	446	2E-1
Ethylbenzene	histological alterations in the liver and kidneys of rats	97.1	291	1E-1
Cumene (isopropylbenzene)	increased kidney weight in rats	110	331	4E-2

[a]Source: U.S. EPA (1997)

Based on structural similarities, cumene might be an appropriate surrogate for the branched-chain alkylbenzenes (sec-butylbenzene and tert-butylbenzene) and ethylbenzene for the straight-chain chemicals (n-butylbenzene and n-propylbenzene). The evidence supporting such an approach is weak because so little data are available for comparison of the activity of these chemicals with that of cumene and ethylbenzene. In particular, there are no pharmacokinetic data to compare sec-butylbenzene and tert-butylbenzene with cumene and n-butylbenzene and n-propylbenzene with ethylbenzene, and data to compare the toxicities of the alkylbenzenes under investigation to cumene and ethylbenzene are limited to acute lethality studies, which can not be used to assess potential critical effects or non-lethal potency. Limited support comes from a comparison of the principal effects and critical effect levels used to derive the RfDs for toluene, ethylbenzene, and cumene. The liver and/or kidneys appear to be the principal target following oral exposure to these chemicals, and the critical effects appear to occur at similar dose levels.

The verified RfD of 4E-2 mg/kg-day for cumene (U.S. EPA, 1997) is based on a NOAEL of 154 mg/kg in female rats receiving 139 gavage doses in a 194-day period (duration adjusted dose of 110 mg/kg-day) (Wolf et al., 1956). The LOAEL was 462 mg/kg (331 mg/kg-day) for increased kidney weight. An uncertainty factor of 3000 was used (10 for subchronic to chronic extrapolation, 10 for interspecies extrapolation, 10 for human variability, and 3 for the lack of reproductive data). Confidence in the principal study was low due to small group sizes. Confidence in the database was also low because the only supporting studies were two inhalation studies. Consequently, confidence in the RfD was low. In deriving a provisional RfD for the branched-chain butylbenzenes (sec-butylbenzene and tert-butylbenzene), an uncertainty factor of 10,000 (10 for subchronic to chronic extrapolation, 10 for interspecies extrapolation, 10 for human variability, and 10 for data base deficiencies for cumene and for the subject chemicals) is

applied to the NOAEL of 110 mg/kg/day. Based on the available acute data and a comparison of the critical effect levels of toluene and ethylbenzene, it does not appear that toxicity is a function of molecular weight for this class of chemicals. Thus, the provisional RfD for sec-butylbenzene and tert-butylbenzene would be 1E-2 mg/kg/day. Confidence in this provisional RfD is very low, reflecting low confidence in the RfD for cumene and the lack of suitable data for the branched-chain butylbenzenes.

The RfD of 1E-1 mg/kg-day for ethylbenzene is based on a NOAEL of 136 mg/kg in female rats administered ethylbenzene via gavage 5 days/week (duration adjusted dose of 97.1 mg/kg-day) for 182 days (Wolf et al., 1956). Histological alterations were observed in the liver and kidneys in rats treated with 408 mg/kg (291 mg/kg-day). The RfD was based on the NOAEL of 97.1 mg/kg-day divided by an uncertainty factor of 1000 (10 to account for use of a subchronic study, 10 for interspecies extrapolation, and 10 to account for human variability). Confidence in the RfD was low which reflected the low confidence in the principal study because only female rats were tested and low confidence in the database because no supporting studies were available. If the RfD for ethylbenzene is used to derive a provisional RfD for n-butylbenzene and n-propylbenzene, then an additional uncertainty factor of 10 should be added to account for the lack of data on n-butylbenzene and n-propylbenzene which could be used to compare it to ethylbenzene. As stated previously, the toxicity of short-chain alkylbenzenes does not appear to be a function of molecular weight, thus adjustment of the RfD does not seem appropriate. The provisional RfD for n-butylbenzene and n-propylbenzene would be 1E-2 mg/kg-day. Confidence in these provisional RfDs would be very low, reflecting the low confidence in the RfD for ethylbenzene and the lack of suitable data for the straight-chain alkylbenzenes under investigation.

REFERENCES

ATSDR (Agency for Toxic Substances and Disease Registry). 1997. Internet HazDat Database: Toxicological Profile Query. (Http://atsdr1.atsdr.cdc.gov:8080/gsql/toxprof.script). U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA.

Dow Chemical. 1954. Results of range finding toxicological tests on sec-butylbenzene. U.S. EPA/OTS Public Files, 8D submission. Microfiche #OTS0515962.

Dupont, 1978. Oral tert-butyl-benzene testing in male rats. U.S. EPA/OTS Public Files, 8D submission. Microfiche #OTS0514883.

Gerarde, H.W. 1959. Toxicological studies on hydrocarbons. III. The biochemorphology of the phenylalkanes and phenylalkenes. AMA Arch. Ind. Health. 19: 403-418.

Gerarde, H.W. and Ahlstrom. 1996. Incomplete reference.

NAS (National Academy of Sciences). 1977. Drinking Water and Health. Vol. I. Printing and Publishing Office National Academy of Sciences, Washington, DC, p. 761-763.
NTP (National Toxicology Program). 1996. NTP Results Report (08/08/96).

NTP (National Toxicology Program). 1997. Chemical Status Report (04/09/97).

Rhone-Poulenc, Inc. 1981. Toxicity studies of tert-butylbenzene and hexamethylene diisocyanate with cover letter dated 07/30/87. U.S. EPA/OTS Public Files, 8D submission. Microfiche #OTS0515465.

RTECS. 1993. Registry of Toxic Effects of Chemical Substances. National Institute for Occupational Safety and Health (NIOSH). Computer database online.

Sandmeyer, E.E. 1981. Aromatic Hydrocarbons. In: Patty's Industrial Hygiene and Toxicology, Vol. IIB, 3rd ed. G.D. Clayton and F.E. Clayton, Eds. New York, NY: John Wiley and Sons. p. 3253-3431.

Shell Oil Company. 1979. Acute oral, percutaneous and inhalation toxicity, skin and eye irritancy and skin sensitization potential of tertiary butyl benzene. U.S. EPA/OTS Public Files, 8D submission. Microfiche #OTS0515724.

U.S. EPA. 1987a. Drinking Water Health Advisory for n-Butylbenzene. Prepared by the Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

U.S. EPA. 1987b. Drinking Water Health Advisory for sec-Butylbenzene. Prepared by the Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

U.S. EPA. 1987c. Drinking Water Health Advisory for tert-Butylbenzene. Prepared by the Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

U.S. EPA. 1987d. Drinking Water Health Advisory for n-Propylbenzene. Prepared by the Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

U.S. EPA. 1991. Office of Health and Environmental Assessment Chemical Assessments and Related Activities. Office of Health and Environmental Assessment, Washington, DC. April 1991. OHEA-I-127.

U.S. EPA. 1994. Office of Health and Environmental Assessment Chemical Assessments and Related Activities. Availability: NTIS. Office of Health and Environmental Assessment, Washington, DC. December, 1994. OHEA-I-127.

U.S. EPA. 1995a. Health Effects Assessment Summary Tables. Annual Update with Supplements. FY-1995. Office of Research and Development, Office of Health and Environmental Assessment, National Center for Environmental Assessment, Cincinnati, OH. PB95-921199.

U.S. EPA. 1995b. Monthly Status Report of the RfD/RfC Work Group (As of 09/01/95). Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH.

U.S. EPA. 1996. Drinking Water Regulations and Health Advisories. Office of Water, Washington, DC. February 1996.

U.S. EPA. 1997. Integrated Risk Information System (IRIS). Online. Office of Health and Environmental Assessment, National Center for Environmental Assessment, Cincinnati, OH.

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzenes. Arch. Ind. Health. 14: 387-398. (Cited in U.S. EPA, 1997).